Unal. Int J Transplant Res Med 2016, 2:017
Volume 2 | Issue 1

International Journal of
Transplantation Research and Medicine

Review Article: Open Access

Skin Lesions after Kidney Transplantation: An updated Review Including Recent Rare Cases

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Abstract

Skin disease is a significant cause of morbidity in chronically immunosuppressed patients, including organ transplant recipients. Cutaneous neoplasms are much more common in renal transplant recipients than in the general population, and are the most common malignancies in these patients. Better surgical techniques and recent advances in immunosuppressive therapy allow patients to survive for many years, free from any complications due to rejection. However, cutaneous lesions can be a significant problem for this group of patients. Immunosuppression predisposes them to infections, as well as malignant tumors. The review of the current literature on skin manifestations in renal transplant recipients is done with emphasis on recent rarely seen clinical manifestations.

Keywords

Renal transplantation, Skin lesions

Introduction

Renal transplantation is the standard form of therapy for patients with end-stage renal failure. The chronic use of immunosuppressants after transplantation with its various side effects, opportunistic infections and the increased risk of malignancies have the potential to affect the skin. Advances in immunosuppressive therapies have resulted in enhanced survival among organ transplant recipients. As a result of a growing population of immunosuppressed patients with prolonged survival, it is imperative that the dermatologists recognize the consequences of long-term immunosuppression and provide appropriate clinical management. Modification of the immune system places these patients at an increased risk for a number of cutaneous conditions, including side effects from the medications themselves, immune-mediated effects from the transplanted organ, opportunistic infections and malignancy. The present study is an attempt to highlight the spectrum of dermatological lesions seen in renal transplant recipients with special emphasis on rarely seen skin lesins, both benign and malignant features.

Mucosal membrane and skin can be affected by immunosuppressive drugs and immunosuppression itself. The spectrum of muco-cutaneous lesions can range from malignancy at one end to infection, iatrogenic lesions, and aesthetic effects on the other end (Table 1). Cutaneous drug reactions may be caused by immunosuppressive therapy that commonly includes corticosteroids, cyclosporine, azathioprine, and antithymocyte and antilymphocyte globulins. Immunosuppressive drugs can also potentiate the effects of other carcinogens, such as ultraviolet radiation, that cause premalignant lesions and skin carcinoma. Opportunistic infections caused by bacteria, fungi, viruses, or protozoa are common in transplant recipients. Skin manifestations of infection in immunosuppressed patients may be an important clue to their presence.

Immunosuppression required to maintain allograft function in kidney recipients results in an impairment of cell-mediated immunity, making these patients prone to a variety of cutaneous infections. A recent review of 134 renal transplant recipients showed that 78% of patients developed cutaneous infections, with the most frequent infections being dermatomycoses, herpes zoster and folliculitis [1]. Both unusual presentations of infection with typical pathogens and infections with rare opportunistic pathogens can make diagnosis and management difficult. Infections may be a primary focus or representations of an underlying disseminated or systemic infection. In the first postoperative month, most infections are related to surgical complications and infections with nosocomial organisms. Wound infections, cellulitis and superficial pyodermas caused by Staphylococcus and Streptococcus are the most common cutaneous infections during this time period. Additionally, atypical pathogens including gram-negative bacteria, fungi and mycobacteria can cause soft tissue and wound infections in these patients. Deep involvement of a primary cutaneous infection can result in necrotizing fasciitis, as well. Reactivation of herpes simplex virus (HSV) occurs with an incidence of 15% - 45% primarily within the first 3 postoperative weeks [2]. The most common manifestation of HSV is orolabial and anogenital lesions.

In the second through fifth post-operative month, infections with opportunistic organisms such as Nocardia, Bartonella and atypical

Table 1: Skin Lesions After Kidney Transplantation.

Aesthetic distorsion
İatrogenic lesions (immunosuppression)
İnfections (Bacterial, viral, fungal, protozoal)
Precancerous lesions (actinic keratosis, warts)
Malignancy (squamous cell ca, basal cell ca, sarcoma, lymphoma, melanoma)

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Citation: Unal E (2016) Skin Lesions after Kidney Transplantation: An updated Review Including Recent Rare Cases. Int J Transplant Res Med 2:017

Received: May 10, 2015: **Accepted:** February 26, 2016: **Published:** February 28, 2016

mycobacterial species are common. Nocardia, a gram-positive, acid-fast rod found in the soil, typically presents as primary pulmonary disease. Cutaneous nocardiosis can present as subcutaneous nodules with pustules, abscesses with sinus tract formation, ulcers, granulomas or lymphocutaneous infection. Infections with the atypical mycobacteria, which include Mycobacterium marinum, M fortuitum, M abscessus, M haemophilum and M avium-intracellulare, have been increasing over the past decade. In a report of Yodmalai et al. a patient with kidney tranplant was admitted to the hospital with prolong fever, dry cough and multiple small erythematous papules on his extremities [3]. A chest X-ray revealed diffuse miliary infiltration. Mycobacterium tuberculosis DNA was demonstrated in bronchoalveolar lavage fluid by polymerase chain reaction. Histopathology of a skin biopsy showed poorly formed noncaseating granulomatous inflammation in the lower dermis and was positive for many acid-fast bacilli. Miliary tuberculosis of the lung and skin were diagnosed. The respiratory symptom and the skin lesions improved after treatment with anti-tuberculous drugs. This study suggests a current rise in the incidence of an old enemy in transplant patients. However, this low incidence may be attributable to a lack of clinical suspicion among practitioners. The spectrum of cutaneous manifestations is diverse and ranges from plaques, to nodules to ulcers. Infection with M marium is typically limited to the skin and lymph nodes, while the rapidly growing M fortuitum, M abscessus as well as M avium-intracellulare and M haemophilum can cause disseminated disease following primary cutaneous infection in transplant recipients, which can result in significant morbidity [4,5]. Mycobacterium leprae disease has also been reported to be seen in kidney transplant recipients [6].

Beyond 6 months of immunosuppression, there is an increased occurrence of infections with viral and fungal pathogens. Reactivation of varicella-zoster virus is common. In a review, the overall incidence of herpes zoster following organ transplantation was 8.6%, with a median time of onset of 9 months [7]. Among these patients, there is a high rate of cutaneous scarring and postherpetic neuralgia as well the potential for dissemination involving multiple dermatomes and risk of reoccurrence. Cytomegalovirus (CMV) is a significant cause of morbidity and mortality. Infection may occur through a primary infection, reactivation of the latent virus or from donor transmission. Symptomatic infection occurs in 20%-60% of transplant patients, and cutaneous involvement is present in 10%-20% of patients and is associated with a poor prognosis [8,9]. Multiple skin morphologies of CMV infection have been reported, and none are pathognomonic. Definitive diagnosis of CMV relies on histological examination.

Human papillomavirus (HPV) is a frequent cause of infection, with an incidence ranging from 25%-50% [10]. HPV infection in recipients has been linked to the development of periungual squamous cell carcinoma (SCC) as well as cancer of anogenital tract. These premalign lesions commonly named as warts (verrucae vulgares and verrucae planae) increases with the duration of immunosuppression with a mean of 15% at 1 year and 85% at 5 years in the literature [11]. They are essentially localized on sun-exposed areas particularly the face and the hands. The lesions are generally multiple. HPV types 1, 2, 3 and 4 are the most frequent, but HPV 6/11 and HPV 16/18, which are potentially oncogenic and normally located in the mucosa of non-immunosuppressed patients, have been described in warts [12]. Epidermodysplasia verruciformis (EV) is a rare genodermatosis associated with a susceptibility to HPV infection and subsequent HPV-mediated oncogenesis. Acquired disease has been described in patients with HIV as well as organ recipients. Clinically, the disease presents as tinea versicolor-like hypopigmented macules or keratotic, flat, wart-like papules [13]. Patients with EV must be closely monitored for development of skin cancer. Molluscum contagiosum may affect both the adult and pediatric kidney recipients. Diagnosis is made based on the characteristic appearance of the centrally umbilicated keratinous plug. Molluscum may be more numerous, larger and refractory to treatment inthose group of patients.

Superficial fungal infections with dermatophytes, in addition to tinea versicolor and onychomycosis are very common among transplanted patients. In a case control study of 102 consecutive renal transplant recipients, pityriasis versicolor was the most common fungal infection (36%), followed by candidiasis (25%) and onychomycosis (12%) [14]. Infection by other opportunistic fungi such as Aspergillus, Cryptococcus, Histoplasma capsulatum, Blastomyces and Coccidioides immitis also can occur, and should warrant an investigation for systemic infection. Cutaneous findings in fungal infections of recipients are non-specific, so direct microscopy and culture of samples are necessary to confirm diagnosis. In the current literature, there are reports of rarely seen fungal lesions, as well. Nouri-Majalan and Moghimi reported a recent a case of cutaneous mucormycosis as a rare entity related to kidney transplantation [15]. It usually presents with ecthyma-like lesions and black necrotic cellulitis. In this study, the authors reported an unusual case of primary cutaneous mucormycosis presenting as erythema-nodosum-like lesions in a woman who had received a renal transplant. Similarly, Yoneda et al. reported cryptococcal necrotizing fasciitis in a patient after renal transplantation [16]. Their patient presented with painful lesions on both lower extremities and fever. At first, bacterial cellulitis was suspected and antibiotic therapy was initiated, but it was not effective. The serum cryptococcal antigen titer was disgnostic, and pathologic examination of debrided tissue and wound pus culture revealed cryptococcal necrotizing fasciitis. Amphotericin B and fluconazole were started, and repeated debridement and skin grafting were performed.

The incidence of skin cancer is increased in transplant recipients as compared to the general population and varies according to the country concerned. Thus, Hartevelt et al. found a cumulative incidence of skin cancer, ranging from 10 to 40 % at 10 and 20 years after transplantation [17]. SCC is the most common cutaneous malignancy among kidney recipients, with a 65-fold increase in incidence compared to the general population [18]. In the general population, basal-cell carcinomas (BCC) are more frequently seen than SCC, but in the transplant population, the ratio of squamous-cell to basal-cell carcinoma in renal transplant recipients is greater than 1. More often, squamous-cell carcinomas develop from warts or actinic keratosis. Other than immunosuppesion, viral agents and sun exposure; genetic factors have also been implicated in the development of skin carcioma in these patients. The information on this point is not yet definite. An association between the class II antigen HLA-DR7 and the occurrence of skin cancers has been described. Conflicting results have been reported concerning HLA-A11: both negative and positive associations have been noted [19]. There is apparently a positive association between HLA B27 and skin cancer [11]. SCC in these patients is highly aggressive and associated with significant mortality. Risk factors for the development of SCC include the duration of immunosuppression, with the risk of carcinogenesis increasing steadily with time post-transplant. Other well-defined risk factors include advanced age at time of transplant, history of skin cancer prior to transplant, history of sun exposure, presence of actinic keratosis.

BCC is the second most common malignancy, with a 10-fold increased risk [20]. The predominance of SCC as the most common subtype of skin cancer is reversed from the immunocompetent population, in which BCC is the most common. The cause of carcinogenesis is multi-factorial including impairment of immuno-surveillance resulting in a reduced host response against tumor cells, oncogenic potential of immunosuppressant drugs, genetic risk factors and viral infections.

Precancerous actinic keratosis progress more often and faster to invasive SCC compared with the general population. Similar to warts, they are located in uncovered areas and they are often associated with warts. The occurrence of an infiltration of the lesion and the rapid recurrence of the lesion are signs of transformation into a squamous-cell carcinoma. Similar to what is found in warts, different types of HPV may be found in association with actinic keratosis. For patients with a limited number of actinic keratosis, cryotherapy or curettage

of individual lesions is the treatment of choice. Many patients have a propensity to develop multiple lesions over a wide area, treatment options for these patients include topical 5-fluorouracil daily or under Unna boot occlusion (chemo-wrap), diclofenac or imiquimod. Photodynamic therapy with a topical photosensitizer has been shown to be more effective [11]. In locally recurrent forms, long-term preventive treatment with topical retinoids should be considered in association with surgery or physical treatment. In diffusely spreading forms systemic administration of retinoids is a treatment option.

The incidence of cutaneous lymphoma in renal transplant patients is currently unknown. Only 10 cases have been reported in the literature [11]. Six were cutaneous B lymphomas and four were cutaneous T lymphomas. These nine lymphomas developed in men. The mean delay after transplantation was 5 years. Cutaneous B-cell lymphomas present with either single or multiple nodules on the skin which frequently ulcerate. The skin lesions are isolated without any visceral involvement. B-cell lymphoma in the oral cavity has also been reported [11]. The patients had erythematous or cyanotic hyperplatic gingival lesions. The infiltrate was composed of lympho-plasmocytoid cells with high mitotic activity. Infiltrating cells were EBV positive. The treatment of choice is radiotherapy. Cutaneous relapse may occur, but visceral metastases have not been reported so far. It has not been proven that reduction of immunosuppressive treatment is effective. Cutaneous T-cell lymphoma patients may present with erythrodermic or haemorrhagic plaques on the legs. Treatment options are corticosteroids, radiotherapy, nitrogen mustard or chemotherapy [21].

The recipients are also at increased risk for cutaneous melanoma, with a 3-5 fold increased incidence compared to the general population. Melanomas represent 14% of skin cancers in patients who received transplants in childhood compared to 5% in adults [11,22]. So, the increase of nevi in children associated with the increase of melanomas suggests immunosuppression begun at an early age may increase the risk of melanoma. Furthermore, a donor with undiagnosed metastatic melanoma can give rise to the development of metastatic melanoma in the recipient. This outcome has been reported in 16 of 20 patients whose donor was found to have metastatic melanoma [11]. Risk factors for melanoma in these patients are similar to those in the general population including the presence of multiple nevi, family or personal history of melanoma and light skin. Current management of melanoma in kidney recipients is similar to that of the general population, with wide local excision with margins based on depth. Patients with nodal or metastatic disease may benefit from reduction in immunosuppression. Overall, survival of recipient patients with melanoma is significantly worse than would be expected in immunocompetent patients, regardless of the Breslow thickness [23].

Other malignant skin tumors affecting kidney transplanted patients include Kaposi's sarcoma and Merkel cell carcinoma (MCC). Kaposi's sarcoma affects between 0.2%-11% of renal transplant recipients, with an increased risk of cutaneous dissemination and visceral spread compared to the general population [24]. The male/female ratio ranges from 2 to 40 with a male predominance similar to that found in other types of Kaposi's sarcoma [11]. Human herpes virus type 8 (HHV8) can be detected by in situ PCR in tissue samples, specifically in mononuclear cells [11,24]. Whether HHV8 is an etiological factor or only an indicator of immunodeficiency is unknown. The average time between transplantation and onset of Kaposi's sarcoma is 20 months [25]. The cutaneous lesions are similar to classical Kaposi's sarcoma and present as dark blue macules which progress to plaques and sometimes to tumors. On the skin, the lesions are mainly located on the trunk and the extremities, rarely on the face. Oral lesions are the most frequent mucous localization, predominantly located on the palate. The most frequent extracutaneous lesions concern lymph nodes, the gastrointestinal tract (mainly stomach and duodenum) and the lungs. Pulmonary involvement is usually seen in the advanced stage of the illness. The risk of mortality from Kaposi's sarcoma is related to the extent of the lesions at presentation. Treatment includes discontinuation of immunosuppressive therapy or changing the treatment regimen to include sirolimus. Imiquimod, interferon alpha and chemotherapy have also been used for treatment of Kaposi's sarcoma with varying degrees of success. MCC is believed to originate from Merkel cells, which are presumably components of the amine precursor uptake and the decarboxylation system (APUD) [26]. MCC, or primary neuroendocrine carcinoma of the skin, is a rare tumor with an aggressive course. The incidence of MCC among recipients is more than 10 times the general population [27]. MCC has a varying presentation but most commonly presents as a blue or red, firm, non-tender, solitary, dome-shaped nodule with rapid growth on the head or extremities. Initial treatment of primary MCC is surgical excision with sentinel lymph node biopsy followed by adjuvant chemotherapy or radiotherapy.

Angiosarcoma is an uncommon malignant tumour accounting for less than 1% of all sarcomas in the general population. Kibe et al. reported the case of an angiosarcoma in a male 12 years after renal transplantation [28]. This lesion was located on the scalp and characterized by multiple violaceous nodules surrounded by poorly demarcated red to purple discoloration. The treatment of this cutaneous tumour is wide excision and possible postoperative radiotherapy.

Mesenchymal cutaneous tumours such as dermatofibrosarcoma protuberans have been seen in rare cases. Lai et al. reported the first case of a patient who developed a dermatofibrosarcoma only 4 years after renal transplantation [29]. This soft tissue tumour is characterized by local recurrence, but only rarely by metastatic spread. A wide and deep excision is necessary to prevent recurrence. Malignant fibrous histiocytomas have also been noted in long-term renal transplant patients [30,31].

In transplant patients, cutaneous metastasis of intraabdominal/thoracic adenocarcinomas should also be questioned. Pontinen et al. has recently reported a case of metastatic skin lesions of pancreatic cancer after kidney transplant [32]. As it is well-known, cutaneous metastases originating from pancreatic cancer are rare. If cutaneous metastases do indeed occur, it is often near the umbilicus, known as the Sister Mary Joseph's nodule. Nonumblical cutaneous metastases are rare, as well. The authors introduced the first reported case of a non-umbilical cutaneous metastatic lesion of pancreatic adenocarcinoma after the transplant of an organ.

In conclusion, it is important to advise patients before transplantation in regard to skin complications, provide regular dermatological follow-up, and tailor immunosuppressive regimen to minimum doses to be compatible with good graft function. The prophylaxis of skin cancers in graft recipients comprises sun protection, information to the patient about the risks of skin tumours and an early treatment of pre-cancerous skin lesions (keratosis, warts). Good cooperation between the specialists is necessary. All transplanted patients should have a dermatological examination at least once a year. All patients seen in the renal transplant outpatient clinic should carefully be examined for any skin lesions. All kidney transplant patients should also be advised to avoid sun exposure, to protect exposed areas with sunscreen or clothing and regularly receive full mucocutaneous skin examinations. If possible, patients should be seen prior to transplantation for identification and management of any pre-existing lesions.

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